REMARKS/ARGUMENTS

After entry of this paper, claims 41-64 are pending. All previously pending claims are cancelled and new claims 41-60 are added. All currently pending claims are drawn to subject matter examined and searched by the Examiner. Support for these claims is found in the original specification and claims and specifically on page 4, lines 27-28; page 5, lines 7-8 and 32-33; page 6, lines 5, 6, 8-10, and 13-14; and in Examples 1-3 and 8. The ratios set forth in new claims 42, 46, 50, 54-58, and 61 and amounts of the components set forth in new claims 53, 58, and 62 were calculated using standard techniques utilized by those skilled in the art and the teachings of the specification, including the examples. No new matter is added by these new claims.

The sole rejection applies to all claims and alleges their non-obviousness over US Patent No. 5,362,718 (Skotnicki), US Patent No. 5,516,770 (Waranis), and UK Patent Application Publication No. 2,327,611 (Haeberlin). Applicants respectfully request reconsideration of this rejection in view of the claim amendments presented herein, the below-noted arguments, and the attached evidence.

With respect, the pending claims are non-obvious over the cited documents. Specifically, the Examiner is incorrect in his assertion that "[o]ne would have been motivated to perfect a parenteral formulation of CCI-779 to reduce the bioavailability uncertainties of other forms of administration (e.g., oral), leading to more accurate and reproducible doses of the agent[1]".

Applicants disagree. One cannot "perfect" a parenteral formulation where there is no existing parenteral formulation. There are significant differences between CCI-779 and rapamycin, including at least two degradation pathways unique to CCI-779 in concentrate (two degradation pathways which are inapplicable to rapamycin). There is no teaching in the art that these pathways exist or that they could be impediments to preparation of a stable CCI-779 parenteral formulation. Thus, there

[1] Page 5, lines 11-14 of the Office Action

could have been no teaching which would have led one to the claimed CCI-779 cosolvent concentrate or formulation.

Not only has the Examiner disregarded the unexpected and advantageous properties of the claimed compositions, but the Examiner has misinterpreted scientific evidence in the specification and post-filing publications which support the non-obviousness of the pending claims. The Examiner has placed the onus on Applicants to provide support of the non-obviousness of the pending claims over the cited art. In response, Applicants now provide a Rule 132 Declaration which contains:

- data evidencing the advantages of the CCI-779 claimed compositions;
- scientific statements demonstrating the advantages of the CCI-779 claimed compositions; and
- data evidencing the differences between rapamycin and CCI-779.

To ensure that Applicants are rebutting each and every of the Examiner's allegation of obviousness of the pending claims, Applicants reproduced each of the Examiner's reason for rejection/obviousness and then provided a rebuttal thereto.

(i) The Examiner made the following allegation in comparing the composition in Example 3 of US Patent Publication No. 2007/0142422 (Rubino) and the instantly claimed compositions.

> Example 3 of Rubino et al...do not disclose any other constituents of the test compositions other than CCI-779 and d,l-α-tocopherol. Thus it is not possible to make a comparison of the effects of d,l-α-tocopherol on the formation of oxidative impurities between the instantly claimed composition (Claim 31) and that which is disclosed in Example 3 of Rubino et al.[2]

Although not specifically recited, the compositions of Example 3 of Rubino contain the components noted in Table A in Point 7 of the attached Rule 132 Declaration. Specifically, the Example 3 Rubino compositions contain CCI-779 (25

[2] Page 6, lines 11-17 of the Office Action

g/mL), d,l-α-tocopherol (0.2%, 0.5%, 1%), anhydrous citric acid (0.025%), dehydrated ethanol (39.5%), and propylene glycol (q.s.). As noted in Point 7 of the Declaration, the compositions of Example 3 lack polysorbate 80 and polyethylene glycol 400. However, as noted in the Declaration, these latter components cannot and do not contribute to degradation of the CCI-779 composition.

Because neither polysorbate 80 nor polyethylene glycol can contribute to degradation, the data and conclusions from Example 3 of Rubino can be utilized to support the pending claims of this application and, therefore, the non-obviousness of the claimed compositions. In view thereof, **it is possible** to make a comparison of the effects of d,l-α-tocopherol on the formation of oxidative impurities between the instantly claimed composition and that in Example 3 of Rubino.

(ii) The Examiner made the following allegation in comparing the composition in Example 3 of Rubino and the instantly claimed compositions.

> ...Example 2 of Rubino et al. (page 8) presents data for three CCI-779 compositions...The results of the study, after disclosed storage times...all showed an increase in oxidative impurities. This suggests that the initial concentration of the impurities has at least as much effect on the formation of additional oxidative impurities as does an excess concentration of d,l-α-tocopherol (i.e., outside the instantly claimed range).[3]

With respect, patent law does not require that claimed compositions be 100% pure, not degrade, or be completely safe.[4] Nor does patent law require that Applicants explain why the claimed compositions are stable and have limited degradation. Instead, Applicants are only required to provide evidence that the same are stable and lack considerable degradation, particularly over those of the cited art. Applicants have done just that.

In addition to the data in the specification and Rubino, the data in the Rule 132 Declaration illustrates that the inclusion of d,l-α-tocopherol in CCI-779

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[3] Page 6, line 18 through page 7, line 11 of the Office Action

[4] MPEP §2164.01(c)

compositions limits the amount of degradation of the composition **regardless of the presence of oxidative impurities**. In fact, the data in the Declaration also demonstrates that CCI-779 compositions containing d,l-α-tocopherol had considerably less TRC, thereby illustrating that the d,l-α-tocopherol significantly controlled escalation of total related components under storage conditions.

Applicants do not dispute that the initial level of oxidative impurities in the claimed CCI-779 compositions may contribute to losses in CCI-779 potency. However, the presence of these initial oxidative impurities does not negate the fact that d,l-α-tocopherol significantly reduces overall CCI-779 degradation.

(iii) The following allegation was made by the Examiner, *i.e.*, that the d,l-α-tocopherol range is not supported by data.

> The instantly claimed range of d,l-α-tocopherol is 0.001% to 0.5%. However, Rubino et al. teaches just three concentrations of d,l-α-tocopherol; 0.2%, 0.5% and 1%, which clearly do not encompass the full range instantly claimed.[5]

With respect, the specification, including the Examples, and the post-filing Rubino provide adequate support for CCI-779 compositions containing the currently claimed range of 0.01% to 0.1% of d,l-α-tocopherol. The mere fact that Rubino does not provide data for d,l-α-tocopherol concentrations below 0.2% does not mean that the same is to be discounted as evidence. Specifically, at the time of the invention, there was no teaching or motivation which would lead one of skill in the art to believe that the d,l-α-tocopherol range of 0.01% to 0.1% w/v would be critical. Specifically, at the time of the invention, one of skill in the art would not have predicted that (a) as little as 0.01% w/v of d,l-α-tocopherol in a CCI-779 composition would stabilize the compositions and (b) amounts of d,l-α-tocopherol in excess of 0.1% w/v in the CCI-779 compositions would be disadvantageous.

As evidence, Applicants point to the scientific comments and data provided in Points 8-10 of the Rule 132 Declaration filed herewith. Specifically, the

[5] Page 7, lines 12-15 of the Office Action

CCI-779 compositions had reduced CCI-779 degradation by-products at all of the d,l-α-tocopherol concentrations, i.e., 0.017% w/v to 0.077% w/v. These data, in conjunction with the data provided in the specification, the teachings in the specification, and knowledge in the art more than demonstrate the 0.01% to 0.1% w/v range for d,l-α-tocopherol, as recited in the pending claims.

In view thereof, Applicant provided evidence, in the form of expert comment and data, that the claimed d,l-α-tocopherol range of the pending claims is critical, *i.e.*, prevents significant CCI-779 degradation.

(iv) The Examiner made the following allegation that it would be obvious to utilize citric acid in the claimed compositions using the teachings of Haeberlin:

> Applicants have not provided a comparison of the instant claims with the closest prior art (e.g., Haeberlin et al.). Page 6 of Haeberlin et al. present comparative results of macrolide degradation in various compositions. The compositions comprise, inter alia, a surfactant, alcoholic solvents, malonic acid and d,l-α-tocopherol (0.1%, which is approximately the middle of the instantly claimed range). The disclosed comparative compositions vary by the presence or absence of malonic acid and the particular macrolide present.[6];
>
> ...it is clear from Haeberlin et al. that one can substitute e.g., citric acid for malonic acid in the disclosed compositions.[7]

The Examiner also made the following allegation that the claimed range of citric acid is obvious using the teachings of Haeberlin:

> The preferred acids [of Haeberlin] include...citric acid...[and] Haeberlin et al. teach a 0.05% to 5% acid concentration range and further disclose that the prepared amount of acid may be determined by routine experimentation.[8]; and

Applicants do not dispute that Haeberlin discusses the instability of macrolides. Haeberlin also makes sweeping statements that "...macrolides are

[6] Page 7, lines 16-22 of the Office Action

[7] Page 9, lines 1-2 of the Office Action

[8] Page 4, lines 12-15 of the Office Action

unstable upon storage..."[9] and notes that 40-O-(2-hydroxy)ethyl rapamycin-2,34-secoacid as a main degradation product of 40-O-(2-hydroxy)ethyl rapamycin.[10] Haeberlin identifies malonic acid and citric acid as agent which may stabilize rapamycin compositions at concentrations higher than provided by the present invention.

Haeberlin lacks any teaching or suggestion of how or why macrolides degrade and certainly does not discuss Applicants' finding that metals are a major factor in the ultimate degradation of rapamycin compounds. In fact, Haeberlin does not even discuss any metals, let alone zinc.

As discussed in the attached Declaration in Point 11, Applicants unexpectedly determined that citric acid chelated zinc impurities in CCI-779 compositions at very low concentrations. By doing so, the CCI-779 compositions were more robust and resisted CCI-779 degradation. Clearly, the motivation to utilize citric acid in the present CCI-779 compositions did not stem from Haeberlin. Therefore, there could not have been, nor was there, motivation to utilize Haeberlin's discussion of citric acid as the impetus to utilize citric acid in the instant CCI-779 compositions.

To further demonstrate the non-obviousness of Applicants' claimed compositions and as the Examiner noted, the compositions of Haeberlin require **at least 0.05%** of acid. On the contrary, Applicants' claimed compositions require **less than 0.01%** of citric acid, which maximum amount is critical and not expected from the teachings of the prior art, including Haeberlin. If anything, Haeberlin teaches away from Applicants' claimed compositions since they include amounts of acid, *i.e.*, excess of 0.05%, that would be detrimental to Applicants' compositions.

(v) The Examiner continues to maintain that it would be obvious to substitute CCI-779 for rapamycin in rapamycin formulations, regardless of the components of the composition.

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[9] Page 3, line 1 of Haeberlin

[10] Page 3, lines 9-10 of Haeberlin

With respect, although both rapamycin and CCI-779 are macrolides and similar in structure, one of skill in the art of macrolides would understand that their interchangeability is not obvious. As evidence, Applicants note the challenges encountered by the inventors in the quest for a stable CCI-779 composition due to the solubility differences between CCI-779 and rapamycin, as discussed in Point 6 of the attached Rule 132 Declaration. Clearly, the Examiner cannot dispute that, the solubilities of rapamycin and CCI-779 are quite different and that the formulation of CCI-779 presents the greater challenge due to the higher doses and concentrations used in clinical trials. In view thereof, one of skill in the art could not have reasonably expected that rapamycin in the compositions of Waranis and Haeberlin could be replaced with CCI-779.

This, in combination, with the difficulties discussed above regarding stabilizing the CCI-779 compositions would not lead one of skill in the art to prepare the claimed compositions.

In summary, Applicants established and provided evidence that the pending lacks are non-obvious over the cited documents. Applicants' claimed compositions have critical features which cannot be ascertained by the cited documents. Specifically, one of skill in the art, armed with the teachings of the Skotnicki, Waranis, and Haeberlin would not have been motivated to prepare Applicants' claimed compositions because:

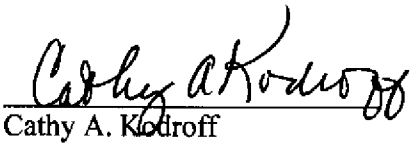
- CCI-779 cannot automatically be substituted for rapamycin in parenteral compositions;
- Applicants' claimed compositions require the specific components noted therein;
- The claimed "less than 0.01%" concentration for citric acid is unexpected, contrary to the teachings of Haeberlin and are critical to providing stable compositions;
- The claimed "0.01% to 0.1%" concentration for d,l-α-tocopherol is unexpected and critical to providing stable compositions;

Thus, the claimed compositions are non-obvious. Withdrawal of this rejection is requested.

The Director is hereby authorized to charge the amount of $1920, charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any overpayment in any fees to our Deposit Account No. 08-3040.

Respectfully submitted,

HOWSON & HOWSON LLP



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